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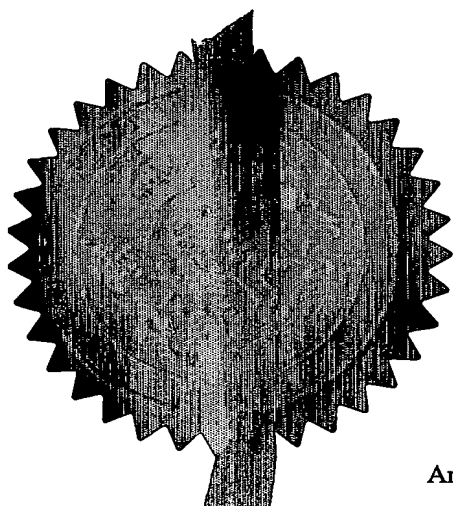
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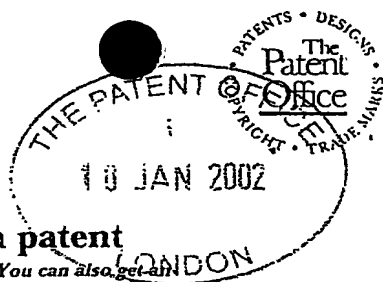
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)



11JAN02 947-1 D10076
P01/7700 0.00-0200502.3

The Patent Office

Cardiff Road
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1. Your reference
62694-011 (KDH)

10 JAN 2002

0200502.3

2. Patent application number
(The Patent Office will fill in this part)

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Natural Science.com Limited
Lindslade House
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Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

8301005001

4. Title of the invention

Pediculicidal Compound

5. Name of your agent (if you have one)

Kathleen Harris
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7 Bishopsgate
London EC2N 3AQ

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

Patents ADP number (if you know it)

8118697001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

None

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

None

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Patents Form 1/77

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Continuation sheets of this form

Description 12

Claim(s) 0

Abstract 0

Drawing(s) 0

10. If you are also filing any of the following, state how many against each item.

None

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Kathleen D Harris

Signature

10 January 2002

Date

12. Name and daytime telephone number of person to contact in the United Kingdom

Kathleen Harris 020 7577 3437

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PEDICULICIDAL COMPOUND

The present invention relates to compounds or compositions particularly suitable for the treatment and prevention of the human head lice, *Pediculus humanis capitis*, as well as
5 other types of lice such as, but not limited to the clothing lice, *Pediculus humanus humanus*.

In general, head lice persists in both developed and underdeveloped countries despite the availability of modern chemical insecticide treatments, public health education, and
10 community based programs of lice eradication. This is often due to a combination of factors. Moreover, there is a school of thought that somehow head lice is a result of bad personal hygiene. This is certainly not the case, as even individuals with a good habit of washing their hair daily may still succumb to a *Pediculus* infestation.

15 Typically the control of infections with head lice has been performed using conventional insecticides. A common example is the use of pyrethrins. Pyrethrins act by rapidly incapacitating insects, often known as "knockdown". Provided that sufficient material is present, the knockdown effect persists until the eventual death of the insect. Normally the effect of the pyrethrins is enhanced or synergised by the
20 addition of piperonyl butoxide to incapacitate the enzymes that the insect would otherwise use to detoxify the pyrethrins. Although pyrethrins have been used as a pediculicidal agent world wide for a number of years (typically in the form of a shampoo), this common insecticide in fact shows a minimal level of activity against louse eggs. For instance, see Burgess, L., "Malathion lotions for head lice a less
25 reliable treatment than commonly believed", Pharm. J. 247: 630-632 (1991). It is believed that the rapid action of the pyrethrins on lice is hindered if there is a prolonged exposure to water and hence why shampoos are believed to be so inadequate. When lice come into contact with large quantities of water they grasp on to the hair reflexively and close their breathing spiracles to avoid being drowned. Since
30 insecticides are really only effective by entry through the spiracles, when the louse

closes their spiracles the insecticide has little chance of creating the knockdown effect. Thus, pyrethrins are essentially regarded as being nonovicidal, but nonetheless are still prevalent in the major products currently available for treating a head lice infestation.

5 Louse eggs are also problematic. The insecticide must make its way through the physical system that is designed to keep out a wide variety of chemical materials and keep water in. The egg shell has a detachable cap that bears a number of air pores that act effectively to exclude fluids, but will allow the passage of gases and it is through these pores that the louse embryo breathes. It is through these very pores that
10 insecticides must also penetrate. Generally the more viscous a fluid is and the greater the surface tension, the less chance of penetration of the egg pores. It is typically believed that aqueous solutions, cream rinses and shampoos have too great a wetting angle for fluid to flow into the pores directly and will only enter if appropriate excipients are included that will wet and allow the solution to flow more readily.

15 In addition to the physical problems in using the most common insecticides, such as pyrethrins, to treat head lice, there is also evidence that these insecticides are resulting in strains of lice which are in fact resistant to one or more insecticides, including treating agents such as malathion, permethrin, phenothrin and piperonal, to name but a
20 few. There is also great concern amongst the public in using harsh chemicals on for instance, young children, pregnant woman or by individuals that may be particularly susceptible or vulnerable to such chemical use.

In view of the difficulties and concerns outlined above, it is an object of this invention
25 to provide an effective and natural pediculicidal composition for treatment of lice infestations, in particular head lice infestations. It is also an object of this invention to provide a compound or composition which will be effective in the prevention of head lice infestation, which is something that the currently available compounds for treating head lice are not believed to accomplish with real effectiveness.

To this end there is provided an improved and extraordinarily effective pediculicidal compound or composition containing active ingredients which are both natural and non-toxic to individuals in need of treatment. In particular, the invention relates to a pediculicidal composition comprising *Melia azadirachta* seed oil, better known as

5 Neem Oil for the prevention and treatment of lice infestation. The oils and other extracts from the Neem tree, *Azadirachta indica*, and closely related species, have been used for centuries as repellent and insecticidal agents for controlling various types of pests, including in protecting agricultural crops, animals and human infestations. In addition, a surfactant is also added with the Neem Oil to maximise the pediculicidal
10 effectiveness of the present invention. The surfactant, cetrimonium chloride, is particularly preferred. Cetrimonium chloride which forms part of the preferred compound of the present invention appears to be acting as a synergizer with the Neem Oil to result in a pediculicidal composition that results in nearly 100% kill rate of both adult lice and eggs. Even though Neem oil has been known as an insecticidal agent, the
15 exact mechanism by which Neem Oil works in "knockdown" of insects is not yet fully understood nor has there ever been developed a formulation based on Neem Oil which is practically 100% effective in eliminating both the lice adults and eggs.

In particular, the invention relates to a pediculicidal compound or composition
20 comprising from about 1% w/w to 1.25% w/w of Neem Oil and from about 0.2% to 0.3 % w/w of surfactant, preferably cetrimonium chloride. Most preferably the formulation consists of 1% w/w of Neem oil and 0.26% w/w of cetrimonium chloride. In addition other ingredients may be included such as those which may also be acting as synergisers with the Neem Oil such as terpenoids, for example, Tea tree oil (i.e. oil or
25 extract of *Melaleuca alternifolia*).

To prevent the tendency of the pediculicidal composition to dry out the skin of the scalp of the patient, an emollient may be incorporated into the compound or composition. Emollients which are particularly preferred are lanolin and polyols such as glycerol,

propylene glycol, sorbitol and low molecular weight polymers thereof. Other examples of emollients are vinyl alcohols and polyvinyl pyrrolidone.

It may also be desirable to add ingredients such as fragrances to make the pediculicidal compound or composition more pleasing to the senses. It is preferred that such fragrances be natural in derivation, although it is not believed to be critical to the effectiveness of the present invention. An example of such a desired ingredient would be lavender oil from the *Lavandula angustifolia* plant. It should be appreciated by the skilled artisan that lavender oil derived from a different species of *Lavandula* may also be included in the pediculicidal compound of the present invention. The addition of these emollients and fragrances is under the proviso that the effectiveness of the active ingredients, Neem Oil and surfactant (or terpenoid) is not lowered or harmed.

A preferred formulation of the present invention comprises the following:

Pediculicidal Compound Ingredients	WT% ACT
Aqua (Water)	91.155
Cetearyl alcohol	4
Glyceryl stearate	2
Melia Azadirachta seed oil (Neem Oil)	1
Propylene glycol	0.675
Cetrimonium chloride 26%	0.26
Melaleuca Alternifolia (Tea Tree) leaf oil	0.25
Lavandula Angustifolia (Lavender) oil	0.25
Urtica Dioica (Nettle) extract	0.2
Methylparaben & Propylparaben & Ethylparaben	0.15
Thymus Vulgaris (Thyme) extract	0.05
Trethanolamine	0.01
	<u>100</u>

It should be appreciated that the "WT% ACT" amounts or quantities do not have to be limited to the specific amounts or quantities listed above. In addition, and as stated above, the ingredients listed in the compound above, such as for example, cetearyl alcohol, *Lavundula angustifolia* (lavender) oil, *Urtica dioica* (nettle) extract, *Thymus vulgaris* (thyme) extract, glyceryl stearate, propylene glycol and trethanolamine may be suitably substituted. As a result of substituting one or more the above ingredients (excluding the substitution of the Neem Oil) the skilled person may therefore need to alter or adjust the percentage composition of the other ingredients accordingly.

10 The number of applications by the infected individual to the scalp with the compound of the present invention is believed to be greatly reduced from previously available remedies and is believed that a single application of the preferred compound listed above may be sufficient to relieve the individual of both adult lice and their eggs.

15 It should also be appreciated by the skilled artisan that the source or supplier of any of the above ingredients is not believed to be important to the efficacy of the present invention.

A comparison of formulations currently on the market for with the present invention, including contra-indications is found in Table 1.

It should also be noted that governmental regulations of certain countries may place limits on the amounts of the above agents to be included in head lice formulations.

25 Experimental Embodiment of the Effectiveness of the Invention

Human lice, *Pediculus humanus*, were obtained from the culture colony maintained by the Medical Entomogy Centre in Fulbourn, Cambridgeshire, United Kingdom. Adult female and male lice, in approximately equal numbers were used for pediculicidal experiments. The lice were fed on the morning of the test and allowed a minimum of 4 hours to recover, during which time they were able to excrete excess water imbibed

with their blood meal. Lice were counted into batches that were provided with squares of open meshed nylon gauze (tulle), as a substrate upon which to stand, and each batch allocated to a marked 30 millimetre plastic Petri dish.

- 5 Louse eggs were obtained by providing actively laying adults with close meshed nylon gauze, as an egg laying substrate over a 48 hour period. After removal of the lice the large pieces of gauze were cut into appropriately sized smaller pieces and allocated on a random basis to marked 90 millimetre plastic Petri dishes.
- 10 Test formulations were compared with a water treated Control group. The ingredients of the formulation tested (the so-called "Nice N' Clear Head Lice Repellent Lotion") against the Control is provided in Table 2.

Pediculicidal tests

- 15 For the test procedure against lice, the gauze bearing the lice was first washed using a 1:15 mixture of Boots (type suitable for frequenting shampooing) and warm tap water. The gauze and insects were then rinsed using approximately 250-300 millilitres of warm (35 ° Celsius) tap water. They were then placed on a medical tissue dampened with tap water to simulate the moistness of washed hair. Sufficient amount of the preferred formulation of the invention was then applied, using the tip of the finger to just coat the lice and gauze. The lice were then returned to their marked Petri dish. The same procedure was repeated for the other replicate gauze squares in the batch.
- 20

- Gauze squares bearing lice were incubated under normal maintenance conditions (30 ° Celsius +/- 2 ° C and 50% +/- 15% relative humidity) until the next day when the record of the mortality was made.
- 25

Ovicidal tests

This test procedure was essentially the same as for the lice apart from the incubation time before recording the results, which was after the eggs in the Control group had complete hatching, approximately 10 day later.

5

Results

Tests of pediculicidal activity showed that the Nice N' Clear formulation tested was active with an overnight application (Table 3). The activity was such that none of the lice demonstrated any sign of life and the majority of them were highly dehydrated with darkening of the tissues due to rupture of the gut.

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A further test was performed in which lice were treated and exposed to the Nice N' Clear formulation for one hour only. The results are located in Table 4.

From the tests it is apparent that the formulation is active against the laboratory lice within a short period of application. However, prolonged application enhances the activity and in practice is more likely to result in elimination of head lice. This is likely because head lice in the wild are normally subjected to a variety of surface active agents used in shampoos and conditioning rinses. In many cases they are also exposed to low doses of herbal extracts contained within such preparations or applied deliberately by carers endeavouring to kill the insects.

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Overnight applications of the formulations to louse eggs also resulted in a high level of mortality (virtually 100%). Complete inhibition of hatching did occur with the Nice N' Clear formulation tested. If one or more of the lice started to hatch, this is designated "Half-hatched" in Table 5. There were no half-hatched louse eggs visible after application with the Nice N' Clear formulation of Table 2. "Undeveloped" for purposes of Table 5 refer to those eggs where a level of inhibition of development of the louse embryos occurs. The inhibition which is very substantial for the Nice N' Clear formulation tested could be due to penetration of one or more components of the

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preparation into the egg structure so that it passed across the chorionic membrane to inhibit development of the embryo inside.

TABLE 1

	ACTIVE INGREDIENT	CONTRA-INDICATIONS	Treatment Time	POP *	F
NICE' N CLEAR	NEEM OIL 1% W/W Cetrimonium Chloride .26%W/W	None	10 mins	✗	✗
DERBAC-M	MALATHION 0.5% W/W	Under 6 months, Pregnant/Breast feeding, Avoid eyes, No repeated use.	12 Hours	✓	✗
LYCLEAR	PERMETHRIN 1% W/W	Under 6 months, Pregnant/Breast feeding, Swallowing.	10 Mins	✓	✗
FULL MARKS Lotion	PHENOTHIRIN 0.2% W/V	Under 6 months, asthma, eczema, swallowing, pregnant/breast feeding, eyes, repeated use, coloured, bleached, permed,	2 Hours	✓	✓
FULL MARKS Mouse	PHENOTHIRIN 0.5% W/W	Under 6 months, eyes, repeated use, asthma, eczema, coloured, bleached, permed, pre- rinsed hair, can cause skin irritation.	30 Mins	✓	✓
PRIODERM Lotion	MALATHION 0.5% W/V	Under 6 months, asthma, eczema, eyes, swallowing, pregnant/breast feeding, repeated use, coloured, bleached, permed, pre-rinsed.	2 Hours + 8 – 10 Hours	✓	✓
PRIODERM Cream Shampoo	MALATHION USP 1.0% W/W	Under 6 months, eyes, repeated use, swallowing, pregnant/breast feeding, coloured, bleached, permed, pre-rinsed hair	5 Mins 3 times at 3 day intervals	✓	✗
QUELLADA-M Liquid	MALATHION 0.5% W/W	Under 6 months, swallowing, can cause skin irritation, eyes, pregnant/breast feeding, permed, pre-rinsed, coloured, bleached hair.	12 Hours	✓	✗
QUELLADA-M Cream Shampoo	MALATHION	Under 6 months, continued prolonged treatment.	5 Mins (Repeat procedure)	✓	✗
SULEO-M	MALATHION 0.5 W/V	Under 6 months, continued prolonged treatment, asthma, eczema, eyes, swallowing.	2 Hours + 8 – 10 Hours	✓	✓
RAPPELL	PIPERONAL	Under 2 years, eyes, swallowing. If asthmatic or have sensitive skin use with caution.	Spray On	✗	✓

* P.O.P = Pharmacy Only Product

TABLE 1 (cont.)

NATRUCLEAR Tea Tree Shampoo	TEA-TREE	Eyes.		10 Mins	✕	✕
BIZNIZ	EUCALYPTUS, ROSEMARY, LAVANDER OILS LISTED.	Under 2 years, epilepsy, pregnant, high blood pressure, eyes, swallowing.		Approx 10 – 15 Mins : leave in conditioner.	✕	✕
CHINESE WHISPERS	CHINESE HERBS				✕	
ASDA HEADLICE REPELLENT LOTION	TEA-TREE & LAVENDER	Details unknown				
XIT – Aromatherapy Spray	T-tree, lavender, eucalyptus, rosemmary, peppermint, west Indian bay / essential oils	Details unknown		Spray on		
XIT – Cleanser, Conditioner & Essential Oil blend liquid	Shampoo = peppermint, lavender, eucalyptus, rosemmary, west Indian bay / essential oils Conditioner = as above + T-Tree Essential oil blend = grapeseed, wheatgerm, avocado t-tree, lavender, eucalyptus oils	Details unknown		30-45 mins		
NITTY GRITTY – Aromatherapy Wet Combing Kit		Details unknown				
NITTY GRITTY – Head Lice Repellent Spray		Details unknown				

NICE 'N CLEAR HEAD LICE REPELLENT LOTION

RM	TRADE NAME	INCI	INGREDIENTS	HAZARD	FUNCTION	AD	ANIMAL TESTED	SUPPLIER	WT % ACT	WT % ACT
0238	Laurex CS; Surfex CS; Cetostearyl Alcohol	Cetearyl alcohol	Cetearyl alcohol	NH	Co-stabiliser & emulsifier.	N	NEVER	Surfachem	4	4
0585	Dehyquart A-CA	Cetrimonium chloride 26%	Cetrimonium chloride 26%	R22,38,41	Cond. & emulsifier	N	1978 Dec	Cognis	1	0.26
1309	Tea Tree Oil Pharmaceutical	Melaleuca Alternifolia	Melaleuca Alternifolia (Tea Tree) leaf oil	NH	Natural	N	NEVER	Paroxite	0.25	0.25
1348	Lavender Oil 40/42	Lavandula Angustifolia	Lavandula Angustifolia (Lavender) oil	NH	Natural	N	NEVER	Connock	0.25	0.25
1895	Nettle Extract	Aqua (Water) 59.4% & Propylene glycol 20% & Urtica Dioica (Nettle) extract 20%	Aqua (Water) 59.4% & Propylene glycol 20% & Urtica Dioica (Nettle) extract 20%	MR36/38	Natural	N	NEVER	A&E Connock	1	0.6
1896	Thyme Extract 21173	Aqua 47.5% & Propylene glycol 47.5% & Thymus Vulgaris (Thyme) extract 5%	Water (Aqua) 47.5% & Propylene glycol 47.5% & Thymus Vulgaris (Thyme) extract 5%	MR36/38	Natural	N	NEVER	Frag Oil	1	0.475
1897	Neem Oil	Melia Azadirachta seed oil	Melia Azadirachta seed oil	NH	Natural	N	1998 Oct	Natural Science. Com Ltd	1	0.475
0117	Nipasept	Methylparaben & Propylparaben & Ethylparaben	Methylparaben & Propylparaben & Ethylparaben	MR36/38/ing; Dirr	Preservative	N	0	Nipa	0.15	0.15
0557	GMS NSE; Lasemul 92N40	Glyceryl stearate	Glyceryl stearate	NH	Emollient & Stabiliser	N	NEVER	Paroxite; Refined	2	2
0177	Trichlanolamine	Trichlanolamine	Trichlanolamine	NH	Buffer	N	1991	Basf	0.01	0.01
0288	Purified Water	Aqua	Aqua (Water)						89.34	89.34
									100	100

Table 3 Activity of Nice'n Clear lotion on human lice

Treatment	Replicate	Number of lice			Mortality % Total (Killed)
		Total	Killed	Moribund	
Nice N' Clear overnight	1	19	19	0	100 (100)
	2	22	22	0	
	3	19	19	0	
Control	1	21	5	0	26 (23)
	2	17	1	1	
	3	19	7	0	

Table 4 Activity of Nice'n Clear lotion on human lice

Treatment	Replicate	Number of lice			Mortality % Total (Killed)
		Total	Killed	Moribund	
Nice N' Clear 1 hour	1	9	1	7	89 (11)

Table 5 Activity of Nice'n Clear lotion on louse eggs

Treatment & application	Replicate	Number of eggs				Mortality %	Undeveloped %
		Total	Hatched	Half-hatched	Undeveloped		
Nice N' Clear overnight	1	132	0	0	5	99.8	4.9
	2	119	1	1	14		
	3	157	0	0	1		
	Total	408	1	1	20		
Control	1	97	64	1	4	29.3	4.7
	2	125	66	3	9		
	3	136	123	1	4		
	Total	358	253	5	17		